

**Remarks**

Reconsideration of this Application is respectfully requested.

Claims 1, 3-10, 13, and 25-50 are pending in the application, with claims 1, 8, 9, 10, 31, 38 and 44 being the independent claims. Support for the amendment to claims 8-10 may be found, *inter alia*, at page 21, lines 11-12 of the specification. No new matter has been added.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

**Priority**

In the Office Action, pages 2-3, the Examiner contends that Applicants have not supplied sufficient proof that establishes that the sequences of SEQ ID NOS:1-3 and 5-7 and the corresponding figures are the same as that found in the priority documents.

As noted by the Applicants in their March 10, 2005 Amendment and Reply, samples of the three biological deposits (ATCC Deposit Nos. 209933, 209934 and 98809) were withdrawn and partial sequences of the deposited cDNAs were generated to verify that the sequences corresponded to currently amended SEQ ID NOS:1-3.

**SEQ ID NOS:1 and 2**

The mouse Dnmt3a and Dnmt3b cDNA clones, represented by SEQ ID NOS: 1 and 2, respectively, were deposited with the ATCC on June 16, 1998, and assigned

ATCC Deposit Nos. 209933 and 209934, respectively. The deposit date of June 16, 1998 was prior to the filing date of the first provisional application, Appl. No. 60/090,906, filed June 25, 1998, the benefit of which is claimed. The '906 application includes the sequence information and references the deposits of the sequenced material on page 15, lines 26, through page 16, line 2, of the specification. SEQ ID NOS:1 and 2 were amended on July 23, 2001, correcting six nucleotides in the coding sequence of SEQ ID NO:1 and two nucleotides in the coding sequence of SEQ ID NO:2. Sequencing of the coding region of ATCC Deposit Nos. 209933 and 209934 confirmed that the coding regions of the mouse Dnmt3a and Dnmt3b clones are the same as the coding regions of amended SEQ ID NOS:1-2. Further, sequencing of ATCC Deposit No. 209934 also revealed that the first 259 *non-coding* nucleotides of SEQ ID NO:2 were not present in the deposited clone.

Applicants submit herewith a Declaration Under 37 C.F.R. § 1.132 by En Li, Ph.D., an inventor, substantiating that, as currently believed, the coding sequences of the cDNA sequences contained within ATCC Deposit Nos. 209933 and 209934 are the same as the coding sequences of currently amended SEQ ID NO:1 and SEQ ID NO:2, respectively. Dr. Li's curriculum vitae is attached to the Declaration as EXHIBIT A. EXHIBITS B and C show a partial nucleotide alignment spanning the coding regions of the cDNA sequence of ATCC Deposit Nos. 209933 and 209934 with currently amended SEQ ID NOS:1-2. The aligned sequences are identical.

***SEQ ID NO:3***

The human DNMT3A cDNA clone, represented by SEQ ID NO:3 was deposited with the ATCC on July 10, 1998, and assigned ATCC Deposit No. 98809. The deposit date of July 10, 1998 was prior to the filing date of the second provisional application, App. No.60/093,993, filed July 24, 1998, the benefit of which is claimed. The '993 application includes the sequence information and references the deposit of the sequenced material on page 16, lines 1-2, of the specification. SEQ ID NO:3 was amended on July 23, 2001, correcting six nucleotides in the coding sequence of SEQ ID NO:3 and deleting the first 123 nucleotides in the 5' non-coding sequence.

The sequencing of the coding region of ATCC Deposit No. 98809 verified that the six nucleotides of SEQ ID NO:3 that were amended on July 23, 2001 were identical to the corresponding nucleotides in the deposited cDNA. Sequencing of the deposited cDNA also revealed a deletion of 46 nucleotides within the coding region of SEQ ID NO:3. The deletion is not present in SEQ ID NO:3 as originally filed in U.S. Appl. Nos. 60/090,906 and 60/093,993, to which priority is claimed. See nucleotides 662-707 of Figure 1C (SEQ ID NO:3) in U.S. Appl. Nos 60/090,906 and 60/093,993.

Applicants submit herewith a Declaration Under 37 C.F.R. § 1.132 by Kenneth D. Bloch, M.D. Dr. Bloch's curriculum vitae is attached to the Declaration as EXHIBIT A. The Declaration substantiates that, as currently believed, and with the exception of the 46 nucleotide deletion described above, the coding region of the cDNA sequence contained within ATCC Deposit No. 98809 is the same as the coding region of currently amended SEQ ID NO:3. Figure 1 of EXHIBIT B shows a partial nucleotide alignment spanning the coding regions of the cDNA sequence of ATCC Deposit No. 98809 and

currently amended SEQ ID NO:3. With the exception of the 46 nucleotide deletion, the aligned sequences are identical.

The 46 nucleotide deletion appears within the coding region of SEQ ID NO:3 at nucleotide position 539-585 as shown in Figure 1 of EXHIBIT B. The Declaration substantiates that a person of ordinary skill in the art would recognize that the 46 nucleotide deletion is an error. First, the deletion found in ATCC Deposit No. 98809 is not present in SEQ ID NO:3 as originally filed or as amended. Second, the deletion is not present in the cDNA sequence of the closely related mouse homolog, SEQ ID NO:1. Third, the deletion causes a frame shift in the reading frame of SEQ ID NO:3 and predicts a truncated protein product compared with that encoded by SEQ ID NO:3 as originally filed and as amended. See Figure 2 of EXHIBIT B. Fourth, the amino acids encoded by the nucleotide sequence downstream of the deletion bear no similarity to the amino acids encoded by SEQ ID NO:3 or the mouse homolog of Dnmt3a, encoded by SEQ ID NO:1. Finally, an examination of the sequence reveals two open reading frames (ORF) in the sequence in different frames. See Figure 3 of EXHIBIT B. The ORFs correspond to the coding sequence of DNMT3A upstream and downstream of the deletion. The presence of two large ORFs in different frames signals to a person of ordinary skill in the art a potential frameshifting sequence error or deletion. All of these factors indicate that the deletion present in ATCC Deposit No. 98809 is an error, and would be recognized as such by a person of ordinary skill in the art.

As noted above, the 46 deleted nucleotides are present in SEQ ID NO:3 as originally filed in the priority documents, and as currently amended. Accordingly, the Declaration thus substantiates that, the combination of ATCC Deposit No. 98809 and

SEQ ID NO:3 as disclosed in the priority documents, conveys to someone skilled in the art the entire nucleotide sequence of amended SEQ ID NO:3.

The Applicants therefore believe, based on the above described Declarations, that they are entitled to the June 25, 1998 filing date for sequences contained within ATCC Deposit Nos. 209933 and 209934 and the July 24, 1998 filing date for the sequences contained within ATCC Deposit No. 98809 and SEQ ID NO:3 as originally filed. Accordingly, Applicants respectfully request that the Examiner acknowledge the Applicants' claim to priority.

***Objections to the Specification***

The Examiner objected to Figures 1A, AB-1 [sic], 1C, 2A, 2B, 2C, 3A and 3B under 35 U.S.C. § 132 as allegedly introducing new matter into the disclosure. The Examiner objected to the Figures as introducing new matter in view of the Applicants' amendments to the Figures to bring them into conformity with the amended sequence listing.

As described above under "**Priority**," the polynucleotides shown in corrected Figures 1A, 1B-1, IC, 2A, 2B, 2C, 3A and 3B have adequate support in the priority documents by reference to the deposits. Thus, no new matter was added to the disclosure by submission of the corrected Figures. Accordingly, Applicants respectfully request that the Examiner withdraw the objection.

***Rejections Under 35 U.S.C. § 112, First Paragraph***

***The First Enablement Rejection***

The Examiner rejected claims 1, 3-7, 13 and 25-50 under 35 U.S.C. §112, first paragraph, allegedly because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. Briefly, the Examiner's contends that the specification does not reasonably provide enablement for variants that have at least 90% sequence identity to polynucleotides that encode SEQ ID NOS:5-8 and arbitrary parts of SEQ ID NOS:1-4 and polynucleotides that encode Dnmt polypeptides.

See Office Action, at p. 4. The Examiner also stated:

[t]he products of the these 90% sequence identical molecules may encode polypeptides that posses function that may not be commensurate with the functions of the native protein. The 90% sequence identical polynucleotides may encode polypeptides that may not maintain the activities proposed in the specifcation. Likewise, subfragments of polynucleotides, SEQ ID NOS:1-4 may not encode polypeptides capable of acting as enzymes which methylate unmodified CpG sites to establish tissue or gene specific methylation patterns, such as wild type DNA cytosine methyltransferases. It would seem that specific function(s) would be required to make the encoded protein useful for the applications disclosed in the specification, such as *in vitro* methylation at the C5 position of cytosine in DNA.

*Id.*, at p. 4-5. Applicants respectfully traverse this rejection.

The Examiner's rejection is almost verbatim to an enablement rejection in a previous Office Action (See paper no. 12, pages 4-6) and is substantively similar to the Examiner's enablement rejection found in the Office Action dated March 10, 2004, where the Examiner alleged that Applicants have not supplied information relative to the

use of the claimed mutants. See p. 6 of Office Action dated March 10, 2004. In the Office Action dated March 10, 2004, the Examiner conceded that "the making of the claimed polynucleotides may not be burdensome" but argued that "the claims do not limit which particular functions they should or should not be able to perform." *Id.* Based on the Examiner's statements, Applicants understood the Examiner's rejection of the claims as not pertaining to the making of the polynucleotide, but rather to the use thereof because there was no limitation on which particular functions the nucleotide molecule performs. In the Applicants' Amendment and Reply filed on March 10, 2005, in order to expedite prosecution and not in acquiescence of the Examiner's rejection, Applicants amended the claims to recite a specific function performed by the polynucleotide, *i.e.*, the function of encoding a polypeptide capable of methylating DNA. Therefore, Applicants believe that the claim amendments made on March 10, 2005 obviate the outstanding enablement rejection.

Based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

#### ***The Second Enablement Rejection***

The Examiner rejected claims 1, 3-10, 24-50 under 35 U.S.C. §112, first paragraph, allegedly because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The Examiner also stated that "Applicants have not supplied information relative to the use of these claimed mutants" and "[t]he claims do not limit which particular functions the mutants should exhibit or

preclude what functions they should or should not be able to perform." Applicants respectfully traverse this ground of rejection.

Applicants note that the Examiner has rejected claims 1, 3-7 and 25-50 in both the first and second enablement rejections in the Office Action, while rejecting claim 13 in the first and claims 8-10 in the second enablement rejection. Applicants further note that the Examiner improperly rejected claim 24, which was previously canceled. It is not clear to the Applicants on what grounds claims 1, 3-7 and 25-50 are rejected that were not mentioned in the first enablement rejection and therefore, Applicants will limit their reply to the second enablement rejection to claims 8-10, having already addressed the rejection to claims 1, 3-7, 13 and 25-50 above.

Solely in an effort to expedite prosecution and not in acquiescence of the Examiner's rejection, the Applicants have amended claims 8-10 to recite isolated oligonucleotide probes or primers. As such, the claims limit the particular functions of the nucleic acid to that of probes or primers and do not suggest that a polypeptide will be produced. The specification discloses that the DNA fragments may be useful as probes or primers for screening or amplifying Dnmt3. See specification at p. 21, lines 11-12; and p. 25, lines 15-29. Therefore, the specification teaches how to make and use the claimed oligonucleotide probes or primers.

Accordingly, Applicants respectfully submit that the claims are enabled by the specification and respectfully request that the Examiner reconsider and withdraw the rejection.

***Rejections Under 35 U.S.C. § 112, First Paragraph (written description)***

The Examiner rejected claims 8 and 10 under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. See Office Action at p. 6. Applicants respectfully traverse this written description/new matter rejection.

Briefly, the Examiner's position is that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. The Examiner relied on *In re Ruschig* as supporting this proposition. *In re Ruschig*, 379 F.2d 990 (CCPA 1967). *Id.* The Applicants respectfully traverse this rejection.

Whether a limitation in a claim satisfies the written description requirement is a factual inquiry and must be assessed on a case by case basis. See *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320 (Fed. Cir. 2000). The *Ruschig* court expressed concern over the extent to which the patentee relied on variables in describing structures, leading that court to explain that rather than blaze marks on trees, the patentee had simply provided the public with a forest of trees. 379 F.2d at 994-995. Applicants submit that the Examiner's reliance on the proposition from *In re Ruschig* is inapplicable because the facts in *Ruschig* are not analogous. The *Ruschig* court held that a description of a genus of compounds indicated by a chemical formula does not disclose an individual compound where there are *several variables* to choose from to arrive at the individual compound. In *Ruschig*, several independent selections of chemical substituents from Markush groups were required to arrive at the individual compound but nowhere in the

specification was the particular selection indicated. 379 F.2d at 993. Because the written description requirement is a factual inquiry and must be assessed on a case by case basis, the relevance of *Ruschig*, if any, is limited to cases where the artisan has to select from several variables to arrive at what is claimed and the specification provides no guidance on making the specific selections. Such a factual scenario is not present here.

The formula on page 21, lines 17-25 of the specification discloses a genus of nucleotide fragments encompassing a range of sizes. The formula does not require the artisan to select from several variables to arrive at the claimed subgenus of fragment sizes. Only one variable is required, and that is the size of the fragment. If the subgenus claimed is discernible in the generalized formula then the written description requirement is met. *In re Driscoll*, 562 F.2d 1245 (CCPA, 1977). Applicants submit that a person of ordinary skill would envision each fragment size in view of the formula because the fragment size is the only variable.

The Examiner's requirement that the Applicants' claimed subgenus be described in *ipsis verbis* is without merit. If the Examiner maintains the rejection for lack of written description, Applicants respectfully request that the Examiner point the Applicants to a case that is at least more factually analogous in order to maintain the rejection, *i.e.* a case that holds that a formula does not describe a subgenus where only one variable is selected to arrive at a subgenus, and provide specific reasons why a person of ordinary skill would not envision each fragment size in view of the formula.

Applicants further resubmit that the specification *expressly discloses* fragments of at least 50 nucleotides of SEQ ID NO:1 as claimed in claim 8. The Applicants respectfully direct the Examiner's attention to page 25 of the specification:

Polynucleotides of the invention which are sufficiently identical to a nucleotide sequences contained in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4, or in the cDNA inserts of ATCC Deposit No. 209933, ATCC Deposit No. 209934, ATCC Deposit No. 98809 or ATCC Deposit No. 326637, may be used as hybridization probes for cDNA and genomic DNA, to isolate full-length cDNAs and genomic clones encoding *de novo* DNA cytosine methyltransferase proteins and to isolate cDNA and genomic clones of other genes that have a high sequence similarity to the *de novo* DNA cytosine methyltransferase genes. Such hybridization techniques are known to those of skill in the art. Typically, these nucleotide sequences are at least about 90% identical, preferably at least about 95% identical, more preferably at least about 97%, 98% or 99% identical to that of the reference. The probes generally will comprise at least 15 nucleotides. Preferably, such probes will have at least 30 nucleotides and may have *at least 50 nucleotides*. Particularly preferred probes will range between 30 and 50 nucleotides.

*Specification* at p. 25, lines 15-29 (emphasis added).

Based on the forgoing, Applicants respectfully request that the Examiner reconsider and withdraw the written description rejection of claims 8 and 10 under 35 U.S.C. § 112, first paragraph.

#### ***Rejections Under 35 U.S.C. § 102***

First, the Examiner rejected claims 1, 3-10, 25-50 under 35 U.S.C. § 102(b) as allegedly anticipated by Okano *et al.* as evidenced by Accession numbers AF068625, AF068626 and AF068627. See Office Action at p. 8. Second, the Examiner rejected claims 1, 3-10, 25-50 under 35 U.S.C. 102(b) as allegedly anticipated by Xie *et al.* as

evidenced by Accession number AF067972. *Id.* at p. 7. Applicants traverse these rejections as they may be applied to the pending claims.

Applicants object to the Examiner's rejection of claim 28, which is directed to an isolated nucleic acid molecule encoding a polypeptide comprising amino acids from about 1-853 in SEQ ID NO:8. Applicants respectfully point out to the Examiner that the polynucleotide encoding SEQ ID NO:8 (*i.e.*, SEQ ID NO:4) is disclosed in the priority application and has not been amended. Thus, it cannot be disputed that SEQ ID NO:4 is entitled to its earliest priority date.

To attest and substantiate that the ATCC deposits corresponding to SEQ ID NOS:1-3 are the same as those disclosed in the PCT and provisional applications, the Examiner suggested submission of a corroborative affidavit or declaration. In an abundance of caution, Applicants have withdrawn samples of the three biological deposits corresponding to sequence contained in SEQ ID NOS:1-3 (ATCC Deposit Nos. 209933, 209934 and 98809) and have sequenced the coding regions of the clones.

As noted above under "**Priority**," Applicants submit herewith Declarations Under 37 C.F.R. § 1.132 by En Li, Ph.D. and Kenneth Bloch, M.D. The Declaration by Dr. En Li substantiates that, as currently believed, the coding regions of the cDNA sequences contained within ATCC Deposit Nos. 209933 and 209934 are the same as the coding regions of currently amended SEQ ID NOS:1-2, respectively. The Declaration by Dr. Kenneth Bloch substantiates that the combination of the coding regions of ATCC Deposit No. 98809 and SEQ ID NO:3 as disclosed in the priority documents is the same as the coding region of currently amended SEQ ID NO:3.

Accordingly, Applicants respectfully submit that Okano *et al.* and Xie *et al.* are not prior art and therefore respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102.

***Rejections Under 35 U.S.C. § 103***

The Examiner rejected claims 1, 3-10, 13, 25-50 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Okano *et al.*, as evidenced by Accession number AF068625, and in view of U.S. Patent No. 6,492,168 B1 ("the '168 patent"). The Examiner also rejected claims 1, 3-10, 13, and 25-50 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Xie *et al.*, and in view of the '168 patent. *Id.*

The Examiner alleges that the '168 patent teaches a polynucleotide complementary to any of SEQ ID NO:5-8 and a method of *in vitro de novo* methylation and that it would have been obvious to one of ordinary skill in the art at the time of the claimed invention to implement a well established and art know method [sic]. *Id.*

First, Applicants respectfully disagree with the Examiner that the '168 patent discloses a nucleic acid sequence complementary to any one of SEQ ID NOS:5-8. As set forth in Applicants Amendment and Reply dated December 9, 2003, SEQ ID NOS:5-8 are polypeptide sequences, and as such, cannot be complementary to polynucleotide sequences. One skilled in the art appreciates that a polynucleotide molecule is "complementary" to another polynucleotide molecule if it forms Watson-Crick base-pairs (e.g., A-T and G-C) at each nucleotide position. Thus, only polynucleotide molecules can be complementary to other polynucleotide molecules as understood by the one of skill in the art. Second, the '168 patent does not disclose any polynucleotide

molecule as claimed in claim 1, or any polynucleotide molecule complementary thereto encoding a polypeptide represented by any one of SEQ ID NOS:5-8.

In view of the attached Declarations under 37 C.F.R. § 1.132, Applicants respectfully submit that Okano *et al.* and Xie *et al.* are not prior art and therefore respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

***Double Patenting Rejection***

The Examiner provisionally rejected claims 1, 3-10, 13, and 25-50 under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-10, 13, 24-37 and 51-55 of copending Application No. 10/623,813. Applicants respectfully traverse the Examiner's rejection.

To further prosecution and not in acquiescence of the Examiner's rejection, Applicants will file a Preliminary Amendment in Application No. 10/623,813 within the next week. Applicants therefore respectfully request that the Examiner reconsider and withdraw the double patenting rejection under 35 U.S.C. § 101.

***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the

outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned directly at (202)772-8637.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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